DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 7/6/10 has been entered.

Status of Application, Amendments and/or Claims

The amendment of 7/6/10 has been entered in full. Claims 1, 4 and 23 are canceled (claims 8-11 and 16-21 were previously canceled). Claims 2, 3, 5, 6, 12, 14 and 15 are amended.

Claims 2, 3, 5-7, 12-15 and 22 are under consideration in the instant application.

Information Disclosure Statement

The Information Disclosure Statement of 7/6/10 has been considered.

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (11/10/09).

All objections and/or rejections of claims 1, 4 and 23 are moot in view of Applicants' cancellation of these claims.

The rejection of claims 2, 3, 5, 12, 13 and 15 under 35 U.S.C. § 102(b) at pg 3-6 as being anticipated by Akira et al (WO 02/06482) is *withdrawn* in view of Applicants' amendments to the claims. Akira et al do not teach a method wherein the test sample is contacted with an isolated cell expressing a TLR9 encoded by a DNA comprising the nucleotide sequence shown in SEQ ID NO: 1.

The rejection of claims 2, 3, 5 and 12-15 under 35 U.S.C. § 102(e) at pg 6-7 as being anticipated by Lipford et al (WO 2004/026888) is *withdrawn* in view of Applicants'

amendments to independent claim 1. Lipford et al do not teach a method wherein the test sample is contacted with an isolated cell expressing a TLR9 encoded by a DNA comprising the nucleotide sequence shown in SEQ ID NO: 1. The nucleotide sequence taught by Lipford et al encodes a TLR9 with four amino acid differences from a TLR9 encoded by a DNA comprising the nucleotide sequence shown in SEQ ID NO: 1. An alignment of the coding region of instant SEQ ID NO: 1 (swine TLR9) with the swine TLR9 protein taught by Lipford et al (SEQ ID NO: 5) is attached to the instant Office Action as Sequence Alignment #1.

The rejection of claims 6, 7 and 22 under 35 U.S.C. § 103(a) at pg 8-12 as being unpatentable over Akira et al (WO 02/06482) and further in view of Kitazawa et al (2003) is *withdrawn* in view of Applicants' amendments to independent claim 5, from which claims 6, 7 and 22 depend.

The rejection of claims 6, 7 and 22 under 35 U.S.C. § 103(a) at pg 12-15 as being unpatentable over Lipford et al (WO 2004/026888) and further in view of Kitazawa et al (2003) is *withdrawn* in view of Applicants' amendments to independent claim 5, from which claims 6, 7 and 22 depend.

New Objections and/or Rejections

Claim Objections

Claims 2 and 5 are objected to because of the following informalities:

(1) Claim 2 is objected to because the abbreviation TLR9 should be accompanied by the full terminology the first time it is used in a series of claims (e.g., "…Toll-like receptor 9 (TLR9)…" Compare with independent claim 5.

(2) Claim 5 is objected to because the term "toll-like receptor 9 (TLR9)" (line 4) should be capitalized as "Toll-like receptor 9 (TLR9)", as used in the specification (e.g., page 3, line 36). Compare also with claims 14 and 15.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6, 7, 12 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 recites the limitation “one or more microorganisms selected in part (d) of claim 5” in lines 2-3. There is insufficient antecedent basis for this limitation in the claim. Specifically, the method steps of claim 5 are limited to "a test microorganism” in the singular; see part (a) and part (d). Thus, part (d) of claim 5 only selects a single test microorganism. Thus, the recitation of "one or more in part (d) of claim 5" lacks antecedent basis in claim 6.

Claim 7 recites the limitation “the one or more microorganisms” in line 1. There is insufficient antecedent basis for this limitation in the claim. Specifically, claim 7 depends from claim 6 and lacks antecedent basis for this recitation for the same reasons as for the parent claim.

Claim 12 recites the limitation “intestinal tract tissue” in line 1. There is insufficient antecedent basis for this limitation in the claim. Specifically, claim 12 limits the intestinal tract tissue of parent claim 2 to intestinal lymphoid tissue. However, parent claim 2 does not contain any limitations that recite “intestinal tract tissue”. This lack of antecedent basis appears to have arisen when claim 12 was amended to depend from claim 2 instead of claim 1 (now canceled), which indicated that the TLR was “intestinal tract tissue expressed” TLR. For purposing of prosecution, claim 12 will be interpreted as encompassing any prior art wherein the TLR9 is an intestinal lymphoid tissue expressed TLR9.

Claim 13 is rejected for depending from indefinite claim 12, and encompassing the same lack of antecedent basis. For purposing of prosecution, claim 13 will be interpreted as encompassing any prior art wherein the TLR9 is an intestinal lymphoid tissue expressed TLR9 wherein the tissue is Peyer’s patch or intestinal lymph node.

Claim Rejections - 35 USC § 112, 4th paragraph

The following is a quotation of the fourth paragraph of 35 U.S.C. 112:

> Subject to the following paragraph, a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

Claims 14 and 15 are rejected under 35 U.S.C. 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim.

See the "Supplementary Examination Guidelines for Determining Compliance With 35 U.S.C. 112 and for Treatment of Related Issues in Patent Applications" (Federal Register, Vol. 76, No. 27, Wednesday, February 9, 2011), pg 7166, section "5. Dependent Claims", which states that "If the dependent claim does not comply the with the requirements of § 112, ¶4, the examiner should reject the dependent claim under § 112, ¶4 as unpatentable rather than objecting to the claim" and "a dependent claim must be rejected under § 112, ¶4 if it omits an element from the claim upon which it depends or it fails to add a limitation to the claim upon which it depends".

Specifically, dependent claim 14 recites the “method of claim 2, wherein the Toll-like receptor is derived from swine”. However, as amended parent claim 2 is limited to a method using a “cell expressing a TLR9 encoded by a DNA comprising the nucleotide sequence shown in SEQ ID NO: 1". The Sequence Listing filed 3/8/2007 indicates that SEQ ID NO: 1 is from *Sus scrofa*, which is pig, a species of swine. Thus, the Toll-like receptor of parent claim 2 is limited to one derived from swine, and dependent claim 14 fails to further limit this subject matter.

Dependent claim 15 recites the “method of claim 2, wherein the Toll-like receptor is Toll-like receptor 9”. However, as amended parent claim 2 is limited to a method using a “cell expressing a TLR9 encoded by a DNA comprising the nucleotide sequence shown in SEQ ID NO: 1". Thus, the Toll-like receptor of parent claim 2 is limited to Toll-like receptor 9, and dependent claim 15 fails to further limit this subject matter.

Therefore, dependent claims 14 and 15 are of improper dependent form because each fails to further limit the subject matter of parent claim 2.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 2, 5 and 12-15 are rejected under 35 U.S.C. 102(a) as being anticipated by Shimosato et al (2003. Biochimica et Biophysica Acta. 1627: 56-61; reference V on the 2/20/09 PTO-892; published 5/13/03 in print and 4/10/03 on-line; see ScienceDirect abstract; http://www.sciencedirect.com/science/article/pii/S0167478103000484). The earliest date to which the instant application claims U.S. priority is 3/5/04, and foreign priority is 6/17/03.

The publication includes several “Inventors/Applicants” in common with the instant application. However, the ‘343 includes a number of additional “Inventors/Applicants” that are not Applicants of the instant application. As stated in MPEP 2132, “The term “others” in 35 U.S.C. 102(a) refers to any entity which is different from the inventive entity. The entity need only differ by one person to be “by others.” This holds true for all types of references eligible as prior art under 35 U.S.C. 102(a) including publications as well as public knowledge and use.”

In independent claim 2, the recitation of “for a sample that activates the intestinal tract immune system” in the preamble of the claim is interpreted as an intended use and bears no accorded patentable weight to distinguish a claimed method over one from the prior art. Shimosato et al teach the sequence of a swine TLR9 (sTLR9) consisting of 1030 amino acids (Figure 1). Shimosato et al further teach that the "nucleotide sequence of swine TLR9 has been submitted to the DDBJ, EMBL and GenBank nucleotide databases under the accession number AB071394" (pg 56, footnote 1). The record for Database GenBank Accession No. AB071394 has been provided by Applicants as reference R1 on the 7/6/10 IDS. An alignment of the nucleotide sequence of AB071394 and instant SEQ ID NO: 1 shows that the two nucleotide sequences are 100% identical (see Sequence Alignment #2 attached to this Office Action). Shimosato

et al further teach transfection of 293T cells with a vector encoding said sTLR9 (pg 58, left column). Shimosato et al further contact said cells with CpG oligodeoxy nucleotides (ODNs) (pg 58, right column), and teach that the ODNs activate the TLR9 receptor (see Abstract and pg 58-59), including detecting intracellular production of "CpG ODN vesicles" (Figure 2c) which is encompassed by the phrase "using signal transduction as an indicator" as recited in part (b) of claim 2. In the results shown in Figure 2 the cells stimulated with the ODNs (panels c and f) were compared to cells in the absence of the ODNs (panels a, b, d and e). Shimosato et al further teach that this shows that "the intestinal immune system mediated by a bacterial DNA through TLR9" (Abstract), which meets the limitation of selecting the test sample as a sample that activates the intestinal tract immune system. Thus, Shimosato et al teach a method comprising (a) contacting a test sample (i.e., ODNs) with an isolated cell (i.e., a 293T cell) expressing a TLR9 encoded by a DNA comprising the nucleotide sequence shown in SEQ ID NO: 1 (i.e., sTLR9); (b) measuring activity of the TLR9 using signal transduction in the cell as an indicator (i.e., intracellular production of CpG ODN vesicles); and (c) selecting the test sample (i.e., ODNs) as a sample that activates the intestinal tract immune system if the activity of the TLR9 is increased as compared to the activity of the TLR9 in a cell not contacted with the test sample. Thus, the teachings of Shimosato et al anticipate claim 2.

In independent claim 5, the recitation of "for microorganisms that activate the intestinal tract immune system" in the preamble of the claim is interpreted as an intended use and bears no accorded patentable weight to distinguish a claimed method over one from the prior art. The CpG oligodeoxy nucleotides (ODNs) taught by Shimosato et al are derived from bacterial DNA, and thus meet the limitation of "an extract from a test microorganism" as recited in claim 5. Thus, Shimosato et al teach a method comprising (a) preparing an extract from a test microorganism (i.e., ODNs); (b) contacting the extract with an isolated cell (i.e., a 293T cell) expressing a TLR9 encoded by a DNA comprising the nucleotide sequence shown in SEQ ID NO: 1 (i.e., sTLR9); (c) measuring activity of the TLR9 using signal transduction in the cell as an indicator (i.e., intracellular production of CpG ODN vesicles); and (d) selecting the test microorganism

(i.e., bacteria producing ODNs) as a microorganism that activates the intestinal tract immune system if the activity of the TLR9 is increased as compared to the activity of the TLR9 in a cell not contacted with the extract. Thus, the teachings of Shimosato et al also anticipate claim 5.

Claims 12 and 13 encompasses a method of claim 2 wherein the "intestinal tract tissue" is "intestinal lymphoid tissue" (claim 12) or Peyer's patch (claim 13, a type of intestinal lymphoid tissue). As described above in the section titled, "Claim Rejections - 35 U.S.C. 112, 2nd Paragraph", these claims are indefinite for lack of antecedent basis in parent claim 2 with respect to "intestinal tract tissue", and for purposes of prosecution have been interpreted as encompassing any prior art wherein the TLR9 is an intestinal lymphoid tissue expressed TLR9 (claim 12) including a Peyer's patch expressed TLR9 (claim 13). Shimosato et al teach that sTLR9 was isolated from Peyer's patches (Pps) of gut-associated lymphoid tissue (GUT). Thus, the teachings of Shimosato et al also anticipate claims 12 and 13.

Claim 14 depends from claim 2 and limits the method to one wherein the Toll-like receptor is derived from swine. As described above in the section titled, "Claim Rejections - 35 U.S.C. 112, 4th Paragraph", claim 14 fails to further limit parent claim 2 because the TLR9 encoded by SEQ ID NO: 1 is a swine TLR9. The teachings of Shimosato et al described above that anticipate claim 2 are directed to a swine TLR9. Thus, the teachings of Shimosato et al anticipate claim 14 for the same reason as claim 2.

Claim 15 depends from claim 2 and limits the method to one wherein the Toll-like receptor is Toll-like receptor 9. As described above in the section titled, "Claim Rejections - 35 U.S.C. 112, 4th Paragraph", claim 15 fails to further limit parent claim 2 is limited to a TLR9 encoded by SEQ ID NO: 1. The teachings of Shimosato et al described above that anticipate claim 2 are directed to a swine TLR9. Thus, the teachings of Shimosato et al anticipate claim 15 for the same reason as claim 2.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3, 6, 7 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shimosato et al (2003. Biochimica et Biophysica Acta. 1627: 56-61; reference V on the 2/20/09 PTO-892; published 5/13/03 in print and 4/10/03 on-line) as applied to claims 2 or 5 above, and further in view of Kitazawa et al (2003. International Journal of Food Microbiology. 85(1-2):11-21; published 15 August 2003 but available on 16 November 2002; 17 pages as printed; cited previously).

Claim 3 depends from claim 2. In claim 3, the recitation of “for producing a pharmaceutical composition that activates the intestinal tract immune system" is interpreted as an intended use and bears no accorded patentable weight to distinguish the claimed method over one from the prior art. Claim 3 further encompasses the method steps of claim 2 and a further step of mixing the selected sample with a pharmaceutically acceptable carrier.

Claim 6 depends from claim 5. In claim 6, the recitation of “for producing a food composition that activates the intestinal tract immune system” in the preamble of the claim is interpreted as an intended use and bears no accorded patentable weight to distinguish the claimed method over one from the prior art. Claim 6 additionally recites a "comprising the method steps of claim 5, and then mixing one or more microorganisms selected in part (d) of claim 5 with a dietarily acceptable carrier".

Claim 7 depends from claim 6, and limits the method to one wherein the one or more microorganisms is a lactic acid bacterium.

Claim 22 depends from claim 6 and limits the method to one wherein the dietarily acceptable carrier is a dairy product acceptable for human consumption (e.g., yogurt).

The teachings of Shimosato et al that anticipate each of independent claims 2 and 5 are described above. Shimosato et al do not teach the additional step of mixing the selected sample with a pharmaceutically acceptable carrier (claim 3), or mixing the

selected microorganism with a dietarily acceptable carrier (claim 6), or the additional limitations that the microorganism is a lactic acid bacterium (claim 7) or that the carrier is a dairy product (claim 22).

Kitazawa et al teach (see Title and Abstract) that an immunostimulatory oligonucleotide with a CpG-like motif (sOL-OB7) exists in the yogurt-producing lactic acid bacterium *Lactobacillus delbrueckii ssp. bulgaricus* (also referred to as *L. bulgaricus*). The art further teaches that said sOL-LB7 immunostimulatory oligonucleotide inherently has the ability to activate cells recombinantly expressing TLR9. Specifically, Shimosato et al (2004) teach "OLLB-7 which is immunostimulatory ODN containing a CpG motif from L. bulgaricus was also injected by CHOK-1^{sTRL9trans} cells (Fig. 1D)" (see page 380 and Figure 1 of Shimosato et al, 2004. Animal Science Journal, 75: 377-382; cited here to provide evidence of an inherent characteristic of the sOL-LB7 oligonucleotide taught by Kitazawa; cited previously). Kitazawa et al further teach that "[t]his study demonstrated that *L. bulgaricus* NIAI B6 was a good candidate of a starter culture for the production of new functional foods" (see Abstract) and "*L. bulgaricus* and its metabolites have been reported to exert a wide variety of immunostimulation ... [t]hese findings together with *L. bulgaricus* containing immunostimulatory oligonucleotides OL-LB7 are useful in the production of new special foods, Namely "Bio-Defense Foods" with contribution to the enhancement of the innate and adaptive immunity" (pg 12). Kitazawa et al further teach the skilled artisan "to expect that sOL-LB7 activates the immune cells through its binding to TLR9 and the activation of possible signaling pathways, like CpG oligonucleotides, although it must be elucidated" (pg 12).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to perform the screening method of claim 1 or 5 as taught by Shimosato et al (with CpG ODNs and an isolated cell expressing a TLR9 receptor), but to substitute an extract (OL-LB7 CpG DNA) from the microorganism (*L. bulgaricus*) taught by Kitazawa et al for the extract (CpG DNA) from a microorganism taught by Shimosato et al, and to further select *L. bulgaricus* as an organism that is assessed as activating the TLR9 receptor, and to further use *L. bulgaricus* to produce yogurt as

taught by Kitazawa, thus mixing said microorganism with a dietarily acceptable carrier that is a dairy product acceptable for human consumption (as encompassed by claims 6, 7 and 22). As the microorganism also comprises the CpG DNA, this would also meet the limitation of mixing the selected test sample with a pharmaceutically acceptable carrier (as encompassed by claim 3). The person of ordinary skill in the art would be motivated to do so because Kitazawa specifically suggests testing to determine if OL-LB7 sequence taught by Kitazawa et al is a TLR9 activating CpG sequence. Such screening would inherently find that the OLLB-7 CpG DNA from *L. bulgaricus* activates the TLR9 receptor as expressed in a cell, resulting in selecting *L. bulgaricus* as a microorganism that is assessed to activate the TLR9 receptor. The skilled artisan would further be motivated to produce yogurt using said microorganism in order to produce a food that would contribute to the enhancement of the innate and adaptive immunity, as taught by Kitazawa et al. Furthermore, a person of ordinary skill in the art would have a reasonable expectation of success in modifying the method Shimosato et al in view of Kitazawa et al because such modification would merely require applying the specific bacteria containing a CpG motif taught by Kitazawa et al to the CpG method taught by Shimosato et al, and further producing yogurt using the bacteria as taught by Kitazawa et al.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Zachary C Howard/
Examiner, Art Unit 1646